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(54) Title: AROMATIC HETEROCYCLIC COMPOUNDS AS ANTI-INFLAMMATORY AGENTS

(57) Abstract

Novel aromatic heterocyclic compounds inhibit cytokines production involved in immunoregulation and inflammation such as interleukin-1 and tumor necrosis factor production. The compounds are therefore useful in pharmaceutic compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory diseases.

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**AROMATIC HETEROCYCLIC COMPOUNDS**  
**AS ANTI-INFLAMMATORY AGENTS**

5    **TECHNICAL FIELD OF THE INVENTION**

The invention relates to aromatic heterocyclic compounds which inhibit the release of inflammatory cytokines such as interleukin-1 and tumor necrosis factor from cells and are thus useful for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease. The invention also relates to processes for  
10 preparing such compounds and pharmaceutical compositions comprising them.

**BACKGROUND OF THE INVENTION**

Tumor necrosis factor (TNF) and interleukin-1 (IL-1) are important biological entities collectively referred to as proinflammatory cytokines. These, along with several other  
15 related molecules, mediate the inflammatory response associated with the immunological recognition of infectious agents. The inflammatory response plays an important role in limiting and controlling pathogenic infections.

Elevated levels of proinflammatory cytokines are associated with a number of diseases  
20 of autoimmunity such as toxic shock syndrome, rheumatoid arthritis, osteoarthritis, diabetes and inflammatory bowel disease (Dinarello, C.A., *et al.*, 1984, *Rev. Infect. Disease* 6:51). In these diseases, chronic elevation of inflammation exacerbates or causes much of the pathophysiology observed. For example, rheumatoid synovial tissue becomes invaded with inflammatory cells that result in destruction to cartilage and bone  
25 (Koch, A.E., *et al.*, 1995, *J. Invest. Med.* 43: 28-38). An important and accepted therapeutic approach for potential drug intervention in these diseases is the reduction of proinflammatory cytokines such as TNF (also referred to in its secreted, cell-free form termed TNF $\alpha$ ) and IL-1 $\beta$ . A number of anti-cytokine therapies are currently in clinical trials. Efficacy has been demonstrated with a monoclonal antibody directed against  
30 TNF in a number of autoimmune diseases (Heath, P., "CDP571: An Engineered Human IgG4 Anti-TNF $\alpha$  Antibody" IBC Meeting on Cytokine Antagonists, Philadelphia, PA, April 24-5, 1997). These include the treatment of rheumatoid arthritis, Crohn's disease

and ulcerative colitis (Rankin, E.C.C., *et al.*, 1997, *British J. Rheum.* 35: 334-342 and Stack, W.A., *et al.*, 1997, *Lancet* 349: 521-524). The monoclonal antibody is thought to function by binding to both soluble TNF $\alpha$  and to membrane bound TNF.

- 5 A soluble TNF $\alpha$  receptor has been engineered that interacts with TNF $\alpha$ . The approach is similar to that described above for the monoclonal antibodies directed against TNF $\alpha$ ; both agents bind to soluble TNF $\alpha$ , thus reducing its concentration. One version of this construct, called Enbrel (Immunex, Seattle, WA) recently demonstrated efficacy in a Phase III clinical trial for the treatment of rheumatoid arthritis (Brower *et al.*, 1997,
- 10 *Nature Biotechnology* 15: 1240). Another version of the TNF $\alpha$  receptor, Ro 45-2081 (Hoffman-LaRoche Inc., Nutley, NJ) has demonstrated efficacy in various animal models of allergic lung inflammation and acute lung injury. Ro 45-2081 is a recombinant chimeric molecule constructed from the soluble 55 kDa human TNF receptor fused to the hinge region of the heavy chain IgG1 gene and expressed in
- 15 eukaryotic cells (Renzetti, *et al.*, 1997, *Inflamm. Res.* 46: S143).

IL-1 has been implicated as an immunological effector molecule in a large number of disease processes. IL-1 receptor antagonist (IL-1ra) had been examined in human clinical trials. Efficacy has been demonstrated for the treatment of rheumatoid arthritis

20 (Antril, Amgen). In a phase III human clinical trial IL-1ra reduced the mortality rate in patients with septic shock syndrome (Dinarello, 1995, *Nutrition* 11, 492). Osteoarthritis is a slow progressive disease characterized by destruction of the articular cartilage. IL-1 is detected in synovial fluid and in the cartilage matrix of osteoarthritic joints. Antagonists of IL-1 have been shown to diminish the degradation of cartilage

25 matrix components in a variety of experimental models of arthritis (Chevalier, 1997, *Biomed Pharmacother.* 51, 58). Nitric oxide (NO) is a mediator of cardiovascular homeostasis, neurotransmission and immune function; recently it has been shown to have important effects in the modulation of bone remodeling. Cytokines such as IL-1 and TNF are potent stimulators of NO production. NO is an important regulatory

30 molecule in bone with effects on cells of the osteoblast and osteoclast lineage (Evans, *et al.*, 1996, *J Bone Miner Res.* 11, 300). The promotion of beta-cell destruction leading to insulin dependent diabetes mellitus shows dependence on IL-1. Some of this damage

may be mediated through other effectors such as prostaglandins and thromboxanes. IL-1 can effect this process by controlling the level of both cyclooxygenase II and inducible nitric oxide synthetase expression (McDaniel *et al.*, 1996, *Proc Soc Exp Biol Med.* 211, 24). Elevation of several cytokines have been demonstrated during active inflammatory bowel disease (IBD). A mucosal imbalance of intestinal IL-1 and IL-1ra is present in patients with IBD. Insufficient production of endogenous IL-1ra may contribute to the pathogenesis of IBD (Cominelli, *et al.*, 1996, *Aliment Pharmacol Ther.* 10, 49). Alzheimer disease is characterized by the presence of beta-amyloid protein deposits, neurofibrillary tangles and cholinergic dysfunction throughout the hippocampal region.

The structural and metabolic damage found in Alzheimer disease is due to a sustained elevation of IL-1 (Holden, *et al.*, 1995, *Med Hypotheses* 45, 559). A role for IL-1 in the pathogenesis of human immunodeficiency virus (HIV) has been identified. IL-1ra showed a clear relationship to acute inflammatory events as well as to the different disease stages in the pathophysiology of HIV infection (Kreuzer, *et al.*, 1997, *Clin Exp Immunol.* 109, 54). IL-1 and TNF are both involved in periodontal disease. The destructive process associated with periodontal disease may be due to a disregulation of both IL-1 and TNF (Howells, 1995, *Oral Dis.* 1, 266).

Proinflammatory cytokines such as TNF $\alpha$  and IL-1 $\beta$  are also important mediators of septic shock and associated cardiopulmonary dysfunction, acute respiratory distress syndrome (ARDS) and multiple organ failure. TNF $\alpha$  has also been implicated in cachexia and muscle degradation, associated with HIV infection (Lahdiverta *et al.*, 1988, *Amer. J. Med.*, 85, 289). Obesity is associated with an increase incidence of infection, diabetes and cardiovascular disease. Abnormalities in TNF $\alpha$  expression have been noted for each of the above conditions (Loffreda, *et al.*, 1998, *FASEB J.* 12, 57). It has been proposed that elevated levels of TNF $\alpha$  are involved in other eating related disorders such as anorexia and bulimia nervosa. Pathophysiological parallels are drawn between anorexia nervosa and cancer cachexia (Holden, *et al.*, 1996, *Med Hypotheses* 47, 423). An inhibitor of TNF $\alpha$  production, HU-211, was shown to improve the outcome of closed brain injury in an experimental model (Shohami, *et al.*, 1997, *J Neuroimmunol.* 72, 169). Atherosclerosis is known to have an inflammatory component and cytokines such as IL-1 and TNF have been suggested to promote the

disease. In an animal model an IL-1 receptor antagonist was shown to inhibit fatty streak formation (Elhage *et al.*, 1998, *Circulation*, 97, 242).

The abnormal expression of inducible nitric oxide synthetase (iNOS) has been

- 5 associated with hypertension in the spontaneously hypertensive rat (Chou *et al.*, 1998, *Hypertension*, 31, 643). IL-1 has a role in the expression of iNOS and therefore may also have a role in the pathogenesis of hypertension (Singh *et al.*, 1996, *Amer. J. Hypertension*, 9, 867).
- 10 IL-1 has also been shown to induce uveitis in rats which could be inhibited with IL-1 blockers. (Xuan *et al.*, 1998, *J. Ocular Pharmacol. and Ther.*, 14, 31). Cytokines including IL-1, TNF and GM-CSF have been shown to stimulate proliferation of acute myelogenous leukemia blasts (Bruserud, 1996, *Leukemia Res.* 20, 65). IL-1 was shown to be essential for the development of both irritant and allergic contact dermatitis.
- 15 Epicutaneous sensitization can be prevented by the administration of an anti- IL-1 monoclonal antibody before epicutaneous application of an allergen (Muller, *et al.*, 1996, *Am J Contact Dermat.* 7, 177). Data obtained from IL-1 knock out mice indicates the critical involvement in fever for this cytokine (Kluger *et al.*, 1998, *Clin Exp Pharmacol Physiol.* 25, 141). A variety of cytokines including TNF, IL-1, IL-6 and IL-
- 20 8 initiate the acute-phase reaction which is stereotyped in fever, malaise, myalgia, headaches, cellular hypermetabolism and multiple endocrine and enzyme responses (Beisel, 1995, *Am J Clin Nutr.* 62, 813). The production of these inflammatory cytokines rapidly follows trauma or pathogenic organism invasion.
- 25 Other proinflammatory cytokines have been correlated with a variety of disease states. IL-8 correlates with influx of neutrophils into sites of inflammation or injury. In consequence, IL-8 has a role in acute respiratory response syndrome (ARDS) and in cerebral reperfusion injury (Matsumoto, *et al.*, 1997, *Journal of Leukocyte Biology* 62: 581). Blocking antibodies against IL-8 have demonstrated a role for IL-8 in the
- 30 neutrophil associated tissue injury in acute inflammation (Harada *et al.*, 1996: *Molecular Medicine Today* 2: 482). Rhinovirus triggers the production of various

proinflammatory cytokines, predominantly IL-8, which results in symptomatic illnesses such as acute rhinitis (Winther *et al.*, 1998, *Am J Rhinol.* 12, 17).

Other diseases that are effected by IL-8 include myocardial ischemia and reperfusion,  
5 inflammatory bowel disease and many others.

The proinflammatory cytokine IL-6 has been implicated with the acute phase response. IL-6 is a growth factor in a number in oncological diseases including multiple myeloma and related plasma cell dyscrasias (Treon, *et al.*, 1998, *Current Opinion in Hematology* 10: 5: 42). It has also been shown to be an important mediator of inflammation within the central nervous system. Elevated levels of IL-6 are found in several neurological disorders including AIDS dememtia complex, Alzheimer's disease, multiple sclerosis, systemic lupus erythematosus, CNS trauma and viral and bacterial meningitis (Gruol, *et al.*, 1997, *Molecular Neurobiology* 15: 307). IL-6 also plays a significant role in  
15 osteoporosis. In murine models it has been shown to effect bone resorption and to induce osteoclast activity (Ershler *et al.*, 1997, *Development and Comparative Immunol.* 21: 487). Marked cytokine differences, such as IL-6 levels, exist *in vivo* between osteoclasts of normal bone and bone from patients with Paget's disease (Mills, *et al.*, 1997, *Calcif Tissue Int.* 61, 16). A number of cytokines have been shown to be  
20 involved in cancer cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with IL-6 receptor antagonists (Strassmann, *et al.*, 1995, *Cytokines Mol Ther.* 1, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha as key factors in both symptom formation and in host defense (Hayden, *et al.*, 1998, *J Clin Invest.* 101, 643). Overexpression of IL-6 has  
25 been implicated in the pathology of a number of diseases including multiple myeioma, rheumatoid arthritis, Castleman's disease, psoriasis and post-menopausal osteoporosis (Simpson, *et al.*, 1997, *Protein Sci.* 6, 929). Compounds that interfered with the production of cytokines including IL-6, and TNF were effective in blocking a passive cutaneous anaphylaxis in mice (Scholz *et al.*, 1998, *J. Med. Chem.*, 41, 1050).  
30 GM-CSF is another proinflammatory cytokine with relevance to a number of therapeutic diseases. It influences not only proliferation and differentiation of stem

- cells but also regulates several other cells involved in acute and chronic inflammation. Treatment with GM-CSF has been attempted in a number of disease states including burn-wound healing, skin-graft resolutiona as well as cytostatic and radiotherapy induced mucositis (Masucci, 1996, *Medical Oncology* 13: 149). GM-CSF also appears
- 5 to play a role in the replication of human immunodeficiency virus (HIV) in cells of macrophage lineage with relevance to AIDS therapy (Crowe *et al.*, 1997, *Journal of Leukocyte Biology* 62: 41). Bronchial asthma is characterised by an inflammatory process in lungs. Involved cytokines include GM-CSF amongst others (Lee, 1998, *J R Coll Physicians Lond* 32, 56).
- 10 Interferon  $\gamma$  (IFN  $\gamma$ ) has been implicated in a number of diseases. It has been associated with increased collagen deposition that is a central histopathological feature of graft-versus-host disease (Parkman, 1998, *Curr Opin Hematol.* 5, 22). Following kidney transplantation, a patient was diagnosed with acute myelogenous leukemia.
- 15 Retrospective analysis of peripheral blood cytokines revealed elevated levels of GM-CSF and IFN  $\gamma$ . These elevated levels coincided with a rise in peripheral blood white cell count (Burke, *et al.*, 1995, *Leuk Lymphoma*. 19, 173). The development of insulin-dependent diabetes (Type 1) can be correlated with the accumulation in pancreatic islet cells of T-cells producing IFN  $\gamma$  (Ablumunits, *et al.*, 1998, *J Autoimmun.* 11, 73). IFN  $\gamma$
- 20 along with TNF, IL-2 and IL-6 lead to the activation of most peripheral T-cells prior to the development of lesions in the central nervous system for diseases such as multiple sclerosis (MS) and AIDS dementia complex (Martino *et al.*, 1998, *Ann Neurol.* 43, 340). Atherosclerotic lesions result in arterial disease that can lead to cardiac and cerebral infarction. Many activated immune cells are present in these lesions, mainly T-
- 25 cells and macrophages. These cells produce large amounts of proinflammatory cytokines such as TNF, IL-1 and IFN  $\gamma$ . These cytokines are thought to be involved in promoting apoptosis or programmed cell death of the surrounding vascular smooth muscle cells resulting in the atherosclerotic lesions (Geng, 1997, *Heart Vessels Suppl* 12, 76). A reduced production of IFN  $\gamma$  is associated with onset of allergic disease in
- 30 infants (Warner *et al.*, 1997, *Pediatr Allergy Immunol.* 8, 5). Allergic subjects produce mRNA specific for IFN  $\gamma$  following challenge with *Vespuila* venom (Bonay, *et al.*, 1997, *Clin Exp Immunol.* 109, 342). The expression of a number of cytokines, including IFN

$\gamma$  has been shown to increase following a delayed type hypersensitivity reaction thus indicating a role for IFN  $\gamma$  in atopic dermatitis (Szepietowski, *et al.*, 1997, *Br J Dermatol.* 137, 195). Histopathologic and immunohistologic studies were performed in cases of fatal cerebral malaria. Evidence for elevated IFN  $\gamma$  amongst other cytokines

5 was observed indicating a role in this disease (Udomsangpetch *et al.*, 1997, *Am J Trop Med Hyg.* 57, 501). The importance of free radical species in the pathogenesis of various infectious diseases has been established. The nitric oxide synthesis pathway is activated in response to infection with certain viruses via the induction of proinflammatory cytokines such as IFN  $\gamma$  (Akaike, *et al.*, 1998, *Proc Soc Exp Biol Med.*

10 217, 64). Patients, chronically infected with hepatitis B virus (HBV) can develop cirrhosis and hepatocellular carcinoma. Viral gene expression and replication in HBV transgenic mice can be suppressed by a post-transcriptional mechanism mediated by IFN  $\gamma$ , TNF and IL-2 (Chisari, *et al.*, 1995, *Springer Semin Immunopathol.* 17, 261).

15 IFN  $\gamma$  can selectively inhibit cytokine induced bone resorption. It appears to do this via the intermediacy of nitric oxide (NO) which is an important regulatory molecule in bone remodeling. NO may be involved as a mediator of bone disease for such diseases as: the rheumatoid arthritis, tumor associated osteolysis and postmenopausal osteoporosis (Evans, *et al.*, 1996, *J Bone Miner Res.* 11, 300). Studies with gene deficient mice have demonstrated that the IL-12 dependent production of IFN  $\gamma$  is critical in the control of

20 early parasitic growth. Although this process is independent of nitric oxide the control of chronic infection does appear to be NO dependent (Alexander *et al.*, 1997, *Philos Trans R Soc Lond B Biol Sci* 352, 1355). NO is an important vasodilator and convincing evidence exists for its role in cardiovascular shock (Kilbourn, *et al.*, 1997, *Dis Mon.* 43, 277). IFN  $\gamma$  is required for progression of chronic intestinal inflammation

25 in such diseases as Crohn's disease and inflammatory bowel disease (IBD) presumably through the intermediacy of CD4+ lymphocytes probably of the TH1 phenotype (Sartor 1996, *Aliment Pharmacol Ther.* 10 Suppl 2, 43). Treatment of patients with IFN  $\gamma$  has demonstrated efficacy in a number of diseases including Behcet's disease which is a multisystem vasculitis. Interestingly in a small patient study for uveitis treatment with

30 IFN  $\gamma$  was essentially ineffective (Kotter, *et al.*, 1996, *Ger J Ophthalmol.* 5, 92). A number of cancers can be treated with IFN  $\gamma$ , this includes the treatment of multiple myeloma. Much of the effect is apparently dependent on IL-6 which is a central

myeloma growth factor (Palumbo *et al.*, 1995, *Leuk Lymphoma* 18, 215). An elevated level of serum IgE is associated with various atopic diseases such as bronchial asthma and atopic dermatitis. The level of IFN  $\gamma$  was negatively correlated with serum IgE suggesting a role for IFN  $\gamma$  in atopic patients (Teramoto *et al.*, 1998, *Clin Exp Allergy* 28, 74).

The work cited above supports the principle that inhibition of cytokine production will be beneficial in the treatment of various disease states. Some protein therapeutics are in late development or have been approved for use in particular diseases. Protein therapeutics are costly to produce and have bioavailability and stability problems. Therefore a need exists for new small molecule inhibitors of cytokine production with optimized efficacy, pharmacokinetic and safety profiles.

#### BRIEF DESCRIPTION OF THE INVENTION

The invention provides novel compounds which inhibit the release of inflammatory cytokines such as interleukin-1 and tumor necrosis factor from cells and which are thus useful for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease.